Current Standards and Emerging Approaches in Glioblastoma

gotoper.com

Dates of certification: *November 30, 2016, to November 30, 2017*
Medium: *Print with online posttest, evaluation, and request for credit*

Faculty

David A. Reardon, MD
Clinical Director, Center for Neuro-Oncology
Physician
Dana-Farber Cancer Institute
Professor of Medicine, Harvard Medical School
Disclosure: *Grant/Research Support - Celldex; Incyte; Midatech. Consultant - Abbvie; Amgen; BMS; Cavion; Genentech/Roche; Merck; Midatech; Momenta Pharmaceuticals; Novartis; Novocure; Regeneron; Stemline Therapeutics. Speaker's Bureau- Merck; Genentech/Roche*

Staff/Planner Disclosures and Conflict of Interest Resolution

The staff of Physicians' Education Resource®, LLC (PER®), and the editorial staff of *The American Journal of Hematology/Oncology®* have no relevant financial relationships with commercial interests to disclose.

It is the policy of PER® to ensure fair balance, independence, objectivity, and scientific objectivity in all of our CME/CE activities. In accordance with ACCME guidelines, PER® requires everyone who is in a position to control the content of an educational activity, including spouses/partners, to disclose all relevant financial relationships with any commercial interest to participants as part of the activity planning process. PER® has implemented mechanisms to identify and resolve all conflicts of interest prior to release of this activity.

Overview
This activity is designed to inform physicians about current and emerging treatment approaches in patients with glioblastoma.

Target Audience
This activity is directed toward medical oncologists, primary care physicians, nurses, and nurse practitioners who treat and/or manage patients with hematologic malignancies. Surgical oncologists, radiation oncologists, pathologists, internists, fellows, physician assistants, and other healthcare providers with an interest in the current topic are also invited to participate.

Learning Objectives
After participating in this CME/CE activity, learners should be better prepared to:

- Discuss the challenges associated with effective drug delivery to patients with glioblastoma
- Summarize the main findings of studies investigating the prognostic and predictive value of O-6-methylguanine-DNA methyltransferase (MGMT) promoter methylation status in patients with glioblastoma
- Characterize the technology currently used to identify MGMT promoter methylation status in patients with glioblastoma
- State the contributions of The Cancer Genome Atlas (TCGA) researchers to the genomic understanding of glioblastoma

Accreditation/Credit Designation
Physicians' Education Resource®, LLC, is accredited by the Accreditation Council for Continuing Medical Education to provide continuing medical education for physicians.

Physicians' Education Resource®, LLC, designates this enduring material for a maximum of 1.0 *AMA PRA Category 1 Credit™*. Physicians should claim only the credit commensurate with the extent of their participation in the activity.

Physicians' Education Resource®, LLC, is approved by the California Board of Registered Nursing, Provider #16669 for 1.0 Contact Hour.

This activity is funded by PER®.

Instructions for Participation/How to Receive Credit:

1. Read the article in its entirety.
2. Use the QR code or type www.gotoper.com/link/1277 into your Web browser to access the posttest.
3. Complete and pass the posttest with a score of 70% or higher.
4. Complete the evaluation and request for credit.

Participants may immediately download a CME/CE certificate upon successful completion of these steps.

Off-Label Disclosure and Disclaimer
This continuing medical and nursing education activity may or may not discuss investigational, unapproved, or off-label uses of drugs. Participants are advised to consult prescribing information for any products discussed. The information provided in this CME/CE activity is for continuing medical and nursing education purposes only and is not meant to substitute for the independent medical judgment of a physician or nurse relative to diagnostic, treatment, and management options for a specific patient's medical condition.

Disclaimer
The opinions expressed in the content are solely those of the individual faculty members and do not reflect those of Physicians' Education Resource®, LLC.

Contact information for questions about the activity:
Physicians' Education Resource®, LLC
666 Plainsboro Road, Suite 356
Plainsboro, NJ 08536
Phone: (888) 949-0045
E-mail: info@gotoper.com

Introduction

Glioblastoma, the most common malignant primary brain tumor in adults, is a highly aggressive cancer associated with substantial morbidity and mortality.[1-8] Despite advances in surgery, radiotherapy, and chemotherapy, current treatment options for glioblastoma remain suboptimal, and patients face a bleak outcome.[4,9,10] Median overall survival (OS) from the time of glioblastoma diagnosis is 12 to 15 months among all patients and only 4 to 5 months among those aged ≥65 years.[2,11,12] Less than 5% of patients with glioblastoma survive beyond 5 years.[13]

Glioblastoma remains one of the most difficult of all human cancers to treat because of its invasive nature and the presence of the blood–brain barrier.[4,7,9,14] Complete surgical removal of glioblastoma is not possible due to invasion of the tumor into surrounding healthy tissue; furthermore, secondary tumor foci may develop close to the resected site.[7] Residual tumor cells are often resistant to standard radiotherapy, and the potential efficacy of radiotherapy is limited by toxicity to healthy tissue.[7] Additionally, the treatment of glioblastoma is complicated by the inability of many drugs administered systemically to overcome the blood–brain barrier and attain adequate concentrations at the site of the tumor.[15]

The current standard of care in younger patients with glioblastoma is maximal safe tumor resection followed by fractionated radiotherapy in combination with concomitant and adjuvant temozolomide therapy.[9,16] A multicenter, randomized, phase 3 study in 573 patients (median age, 56 years) with newly diagnosed glioblastoma showed that the addition of temozolomide to radiotherapy was associated with a statistically significant survival benefit compared with radiotherapy alone.[17] At median follow-up of 28 months, median survival was 14.6 months in patients receiving radiotherapy plus temozolomide and 12.1 months in those receiving radiotherapy alone; the 2-year survival rate was 26.5% and 10.4%, respectively.[17]

The current standard of care in elderly patients with glioblastoma remains a matter of debate; therefore, until a consensus is reached, current therapeutic options (ie, surgery, radiotherapy, and temozolomide) should be utilized based on patient-specific factors and patient preference.[2] In a phase 3 study investigating radiotherapy regimens in elderly and/or frail patients with newly diagnosed glioblastoma, short-course radiotherapy (25 Gy in 5 daily fractions over 1 week) and commonly used radiotherapy (40 Gy in 15 daily fractions over 3 weeks) were shown to result in similar median progression-free survival (PFS), median OS, and quality-of-life outcomes.[18] A systematic review of the medical literature to identify articles containing survival data in elderly patients with glioblastoma who were treated with either temozolomide alone or radiotherapy alone between 2005 and 2013 showed support for the use of hypofractionated radiotherapy or temozolomide monotherapy.[19] Of interest, the literature review also showed variability in the definition of elderly and a lack of randomized clinical studies comparing temozolomide alone with radiotherapy alone in elderly patients with glioblastoma.[19]

As noted above, radiation therapy is a critical component in the treatment of glioblastoma.[3,20] In 2016, the American Society for Radiation Oncology (ASTRO) published evidence-based clinical practice guidelines for the use of radiation therapy in patients with glioblastoma to help facilitate treatment decision-making.[3,20] The ASTRO guideline focuses on (1) indications for the use of radiation therapy after biopsy/resection and the ways in which systemic therapies modify the effect of radiation therapy; (2) the optimal dose-fractionation schedule for external beam radiation therapy after biopsy/resection; (3) ideal target volumes for curative-intent external beam radiation therapy; and (4) the role of re-irradiation in disease recurrence after completion of standard front-line therapy.[3,20]

The methylation status of the promoter of the O-6-methylguanine-DNA methyltransferase (MGMT) gene is a prognostic and predictive biomarker in glioblastoma.[21] Inactivation of MGMT by promoter methylation has been shown to be associated with longer survival in patients with glioblastoma who are treated with radiation and temozolomide.[22-24] In a phase 2 study in 38 patients with glioblastoma who underwent resection and were treated with radiation and temozolomide, 18-month survival was 62% versus 8% in patients with methylated and unmethylated MGMT promoters, respectively.[23] A study evaluating the effect of MGMT promoter methylation status in 206 patients with glioblastoma who received either radiotherapy alone or radiotherapy combined with concomitant and adjuvant treatment with temozolomide found that MGMT promoter methylation was an independent favorable prognostic factor irrespective of treatment assignment.[24] In the study, OS was 15.3 months in patients with a methylated MGMT promoter versus 11.8 months in those with an unmethylated MGMT promoter in the cohort receiving radiotherapy alone and 21.7 versus 12.7 months, respectively, in the cohort receiving radiotherapy in combination with temozolomide.[24] Of interest, data have also shown that unmethylated MGMT promoter status is associated with unfavorable clinical outcome in a subpopulation of patients with non-resectable glioblastoma after adjuvant therapy.[25]

Data from two clinical trials support consideration of MGMT methylation status in older patients with glioblastoma to aid in treatment decision-making.[26-28] In the phase 3 Nordic

trial, which randomized 291 patients aged ≥60 years with newly diagnosed glioblastoma to temozolomide, hypofractionated radiotherapy, or standard radiotherapy, OS was significantly longer in temozolomide-treated patients with a methylated MGMT promoter than in those with an unmethylated MGMT promoter (9.7 vs 6.8 months, respectively); however, no difference in OS was observed in patients with methylated and unmethylated MGMT promoters who were treated with radiotherapy (hazard ratio, 0.97).[27] In the randomized phase 3 NOA-08 study, which randomly allocated 373 patients aged >65 years with anaplastic astrocytoma or glioblastoma to temozolomide alone or radiotherapy alone, OS was longer in those with MGMT promoter methylation than without MGMT promoter methylation (11.9 vs 8.2 months, respectively).[28] Event-free survival was longer in patients with MGMT promoter methylation who received temozolomide than in those who received radiotherapy (8.4 vs 4.6 months, respectively); however, the opposite was true in patients with an unmethylated MGMT promoter (3.3 vs 4.6 months, respectively).[28]

Researchers recently conducted a retrospective analysis of all MGMT promoter methylation testing performed at the Center for Advanced Molecular Diagnostics between 2009 and 2013 to investigate the clinical implication of inconsistently methylated results from glioblastoma tumor samples on replicate methylation-specific polymerase chain reaction (PCR) testing.[21] MGMT test results were reported as methylated, unmethylated, or inconsistently methylated.[21] An inconsistently methylated result was defined as one in which a methylated peak was noted in some but not all replicates from a single DNA sample.[21] In brief, the analysis showed that (1) inconsistently methylated results occurred in 12% of cases; (2) inconsistent methylation was correlated with relatively poor OS; and (3) a dose-response association may exist between OS and the degree of methylation across replicates in the inconsistently methylated cases.[21]

The most suitable method of clinical MGMT testing remains unclear, as numerous assays have been associated with suboptimal analytic performance.[16] Additionally, the measurement of MGMT is not standardized, which leads to a high degree of variability in test results.[5] Although MGMT testing has been promoted in patients with glioblastoma, inaccessibility and cost limit its use in general clinical practice.[5] A recent study described the first validated pyrosequencing-based MGMT methylation test using clinical formalin-fixed paraffin-embedded biopsy tissue from 33 patients with glioblastoma.[29] A meta-analysis of 11 studies conducted to evaluate the prognostic value of MGMT promoter status in patients with glioblastoma using a pyrosequencing assay showed that methylation positivity is associated with increased survival.[8]

Nearly all glioblastomas recur,[13] and treatment options are limited in patients with recurrent disease.[1] In 2009, the anti-angiogenic agent bevacizumab was granted accelerated approval by the FDA for use as monotherapy in patients with recurrent glioblastoma based on data from two phase 2 studies.[13] In the multicenter, open-label, non-comparative AVF3708g study, which included 167 patients with recurrent glioblastoma who received bevacizumab with or without irinotecan, estimated 6-month PFS was 42.6% in the bevacizumab arm and 50.3% in the bevacizumab/irinotecan arm; median OS was 9.2 and 8.7 months, respectively, and the objective response rate was 28.2% and 37.8%, respectively.[30] In the second pivotal study, which included 48 heavily pretreated patients with recurrent glioblastoma who received single-agent bevacizumab, median PFS and median OS were 16 weeks and 31 weeks, respectively; the 6-month PFS and OS rates were 29% and 57%, respectively.[31] In general, the use of bevacizumab has been associated with a reduction in cerebral edema, improvement in neurologic symptoms, and a reduction in corticosteroid usage[31]; however, once a patient becomes refractory to bevacizumab, median OS is approximately 1.1 to 4.5 months irrespective of the treatment strategy used.[1,32,33]

A biodegradable polymer wafer containing carmustine was approved by the FDA in February 1997 for implantation in patients with recurrent glioblastoma as an adjunct to surgery.[34] FDA approval was based on data from a placebo-controlled study in which median survival in patients with malignant recurrent gliomas was 31 weeks in those receiving carmustine wafer implantation and 23 weeks in those receiving placebo implantation.[35] A recent meta-analysis evaluating survival outcome in patients with recurrent high-grade glioma found that median OS was 9.7 months in those who received carmustine wafer implantation versus 8.6 months in those who did not receive such treatment; 2-year OS was 15% and 12%, respectively.[36] In February 2003, the indication for carmustine wafer was extended to include implantation in patients with newly diagnosed high-grade malignant gliomas as an adjunct to surgery and radiation.[34] At present, many patients who have received carmustine wafer implantation are excluded from clinical trial participation due to concerns about potential toxicities, confounding of results, and a lack of reliable survival data.[36]

Optune (previously known as NovoTTF-100A), a portable device approved by the FDA to treat adults with recurrent and newly diagnosed glioblastoma, delivers tumor-treating fields (TTFs) to selectively disrupt mitosis via noninvasive transducer arrays.[1,37,38] In April 2011, Optune was approved as monotherapy, and as an alternative to standard medical therapy after surgical and radiation options have been exhausted, in patients with histologically or radiologically confirmed recurrent

glioblastoma in the supratentorial region of the brain after receiving chemotherapy.[39] In the randomized phase 3 EF-11 study, which investigated the efficacy and safety of TTF alone versus physicians' choice of chemotherapy in patients with recurrent glioblastoma, median OS was 6.6 and 6.0 months, respectively, and 1-year survival was 20% in both treatment arms.[40] In general, TTF was associated with lower toxicity and greater improvement in quality of life compared with chemotherapy; the most commonly reported TTF-related adverse events were mild to moderate skin reactions.[40] Of interest, a post hoc analysis of data from the pivotal EF-11 trial found that median OS was significantly higher in patients receiving ≥1 course of TTF therapy compared with those receiving physicians' best choice of chemotherapy (7.7 vs 5.9 months, respectively).[33] Analysis of data from a post marketing registry of 457 patients with glioblastoma who received treatment with the NovoTTF-100A system between October 2011 and November 2013 in a US clinical practice setting showed that median OS was 9.6 months, and 1-year and 2-year survival rates were 44% and 30%, respectively.[6] In April 2015, the indication for Optune was expanded to include the treatment of adults with newly diagnosed, supratentorial glioblastoma in combination with temozolomide following maximal debulking surgery and completion of radiation therapy together with concomitant standard of care chemotherapy.[38,39]

Data from several retrospective uncontrolled case series and a post hoc analysis of the registration trial for temozolomide have shown that the use of valproic acid improved survival in patients with newly diagnosed glioblastoma; however, other analyses suggest that antiepileptic drug use does not confer a survival benefit in such patients.[41] For example, in a pooled analysis of data from four prospective randomized clinical trials that included 1869 patients with newly diagnosed glioblastoma, PFS and OS in patients receiving valproic acid at chemoradiotherapy initiation was not improved compared with those not receiving valproic acid (hazard ratios for PFS and OS = 0.91 and 0.96, respectively).[41] In addition, PFS and OS in patients receiving valproic acid at chemoradiotherapy initiation, as well as after chemoradiotherapy, did not differ from those not receiving valproic acid at both of these time points.[41] Furthermore, no correlation with improved survival outcome was noted with the use of the antiepileptic drug levetiracetam.[41]

In recent years, much progress has been made in understanding the molecular landscape in glioblastoma due to the efforts of The Cancer Genome Atlas (TCGA) research network, a collaborative initiative jointly funded and managed by the National Cancer Institute and the National Human Genome Research Institute, both of which are part of the National Institutes of Health.[42] The TCGA was established to comprehensively catalogue somatic genomic changes in more than 25 different cancer types, the first of which was glioblastoma.[42] The systematic genomic analysis of tumor samples by the TCGA has led to the discovery of genetic mutations and DNA alterations that could help to elucidate important biological pathways relevant for the diagnosis and treatment of glioblastoma.[42-45] Furthermore, an enhanced understanding of the relationship between the tumor microenvironment and the immune system has generated much interest in the use of immunotherapeutic strategies to improve outcome in patients with glioblastoma.[4,10,46] Several immunotherapies, including checkpoint blockade, cancer vaccines, adoptive T-cell immunotherapy, and oncolytic virotherapy, are currently being investigated in glioblastoma clinical trials based on promising preclinical data.[4,9,47,48] In particular, the development of agents that target immune checkpoint pathways in glioblastoma has garnered much attention, but numerous challenges have also been acknowledged, including the lack of standardized and validated assays to measure immune response and how best to manage immune-related adverse events in the central nervous system.[46] Recent data suggest that an effective treatment strategy in glioblastoma will likely require the use of combination therapy (ie, surgery, chemotherapy, radiation and immune stimulatory approaches)[4] with appropriate consideration of dosage, toxicity, and sequencing.[46]

David A. Reardon, MD, Clinical Director of the Center for Neuro-Oncology at the Dana-Farber Cancer Institute (Boston, MA) offered his insights on current and emerging treatment approaches in patients with glioblastoma.

Moderator: Would you discuss the prognostic and predictive value of MGMT promoter methylation status in patients with glioblastoma?

Dr. Reardon: MGMT is a validated biomarker for patients with glioblastoma undergoing our current standard of care therapy with radiation and temozolomide. MGMT effectively neutralizes the DNA-damaging effect that temozolomide renders in cancer cells and allows them to basically be resistant to chemotherapy. Data have clearly demonstrated, now prospectively, that patients whose tumors have MGMT promoter methylation—which effectively turns expression of the gene off, leading to a low level of this enzyme in the tumor—have a better outcome in terms of PFS and OS with the current standard of care therapy relative to patients whose tumors have an unmethylated MGMT promoter in which the MGMT gene is expressed and associated with a higher level in tumor tissue.

Studies have shown that patients who have an MGMT-methylated promoter have significantly longer survival with our current standard of care therapy than do patients who have an

unmethylated promoter. The studies that have been done show that in unmethylated patients, median PFS and median OS are only 0.9 months longer with the addition of temozolomide compared with radiation therapy alone. So, these statistics show the averages, or the median, and it's important to elaborate that the value of this MGMT testing is helpful, but it's not a perfect biomarker. In other words, a number of my patients over the years have had an MGMT tumor level that is low due to a methylated promoter, but unfortunately, they have not responded well to the current standard of care therapy. Conversely, there are patients in whom the gene level is high due to lack of methylation of the promoter, and they have done quite well. So, we use the test as a predictor, a general predictor, but it is by no means 100 percent sensitive. There are plenty of exceptions on either side. And, part of the reason for that, I think, is related to the way that the MGMT level of the tumor is evaluated.

Moderator: What technology is currently used to identify MGMT promoter methylation status in patients with glioblastoma? Does the technology differ in research versus clinical settings?

Dr. Reardon: A variety of different techniques are currently used to identify MGMT-promoter methylation status, including methylation-specific polymerase chain reaction (MSP), a MethyLight assay, pyrosequencing, methylation-specific multiplex ligation-dependent probe amplification, and protein immunohistochemistry to detect the actual MGMT protein in surgical tumor specimens. The MSP technique, or methylation-specific reverse-transcriptase PCR, is the gold standard or the standard way of evaluating MGMT. But, the variability of the tests that are done, as well as the challenges associated with each assay and the heterogeneity of tumor tissue, can make interpretation of MGMT quite challenging. How best to accurately define the MGMT status of a tumor remains a controversial area in glioblastoma research. But, at this point, I think that it's fair to say that with any of these assays, there are clearly negative tumors, there are clearly positive tumors, and there are a number of tumors that fall in the middle, where it can be challenging to know where to draw the line in terms of discriminating them as an MGMT-low or an MGMT-high tumor, depending on the assay that is used.

Moderator: ASTRO recently published evidence-based clinical practice guidelines on the use of radiation therapy in patients with glioblastoma. Would you highlight some of the most important recommendations?

Dr. Reardon: I think that the ASTRO guidelines are an important document for the neuro-oncology community because they provide a consensus established by a panel of experts with significant experience in the treatment of glioblastoma. These guidelines can be incorporated and utilized at all levels—both the academic and community level—to help guide practitioners in how best to apply a critical cornerstone of therapy, radiation therapy, into the care plan for patients with glioblastoma.

The panel of experts discussed a variety of different areas that will help provide some guidance. One area, in particular, was defining the optimal dose-fractionation schedule after biopsy/resection for patients with glioblastoma—what to consider for radiotherapy relative to a patient's chronologic age as well as physiologic age. There are variations now in radiation therapy that are being applied and appropriately considered for chronologically elderly patients (those older than 70 years of age) who have a decent performance status, where a hypofractionated dosing schedule, typically around 40 Gy, is administered over 3 weeks, as opposed to the standard 60 Gy administered over 6 weeks.

The panel also discussed some of the issues related to ideal target volumes. There has been some debate about that topic amongst radiation oncologists over the last several years, and the data and literature regarding target volumes were summarized in guidance provided in the paper. Finally, the guidelines concluded with commentary on the role of re-irradiation, a practice that has gained significant interest and is becoming increasingly utilized in the care of patients following progression after initial standard-of-care therapy. So, our hope is that this guidance will be very helpful across the spectrum of practitioners involved in the care of patients with glioblastoma, specifically with regard to some of these issues.

Moderator: Would you describe the contribution of TCGA researchers to the genomic understanding of glioblastoma?

Dr. Reardon: TCGA has fortunately prioritized the evaluation of glioblastoma tumors. The TCGA was initially launched by the National Institutes of Health in 2005 and utilizes state-of-the-art genomic sequencing, bioinformatics, and integrated multidimensional platforms to catalogue and discover genetic factors associated with different cancers. The platforms include genomic next-generation DNA sequencing involving RNA sequencing for transcriptomic evaluation, epigenomic data evaluating DNA methylation sequencing, and proteomics using reverse-phase protein array analyses.

TCGA has currently evaluated more than 33 different human tumor types and more than 11,000 tumor normal tissue matched paired samples. All of the data from these analyses are publicly, freely available in datasets to help drive and stimulate research. TCGA, in the initial phase of effort, which ran from 2005 to 2008, focused on three very poor-prognosis

tumor types—glioblastoma, lung cancer, and ovarian cancer—to initiate this multiplatform analysis. A $50 million investment was utilized to get this work up and running. During phase 2, which was initiated in 2009, the work has continued to expand and to include an additional 30 different tumor types. TCGA has contributed very significant information regarding the biology of glioma and glial tumors in glioblastoma, including the characterization of genetic mutations and dysregulated cell signaling pathways in now 2000 to 3000 glioblastoma tumor samples.

Glial tumors have been identified by looking at a variety of these different methodologies—the genomics, the transcriptomics, proteomics, and methylation profiling—which has really given us remarkable insight into the biology and the heterogeneity of these tumors. We have identified many different targetable mutations and dysregulated cell signaling pathways for therapeutic exploitation and dramatically increased our understanding of the biology and the physiology of glial tumors. So, the TCGA I'd have to say is probably the most important effort that has contributed to our understanding of the biology of glioblastoma tumors in the last 10 years.

Moderator: What targeted agents, immunotherapeutic agents, and vaccines currently being investigated in glioblastoma are of greatest interest to you?

Dr. Reardon: We've gone through several eras of therapeutic intervention, if you will, in the treatment of this disease. In the early 2000s, cytotoxic chemotherapeutics were heavily investigated, and this era of clinical research led to the identification of temozolomide as a chemotherapy that was able to get into the brain and have an impact on glioblastoma.

The second era, I think, began, thereafter, looking at some of the locally administered therapies to try to bypass the blood–brain barrier and administer therapies directly into the tumor. This led to the development and approval of the carmustine-impregnated polymer wafer Gliadel, which is currently available and utilized, placed in the resection cavity of patients. In this era, there was also a lot of interest in developing therapies locally administered into the tumor by convection-enhanced delivery. The next era of therapeutic development began to take advantage of some of the data identified through the TCGA work, identifying specific mutations that were frequently identified in tumors, as well as dysregulated cell signaling pathways, primarily the PI3K/Akt pathway due to PI3K activation or PTEN loss. And, along with other cancer indications, the era of targeted therapies began for glioblastoma tumors. Not long thereafter, targeting angiogenesis became quite a high level interest, not only for glioblastoma but across the spectrum of different cancer indications. I think that each of these treatment eras has led to a lot of information and a lot of experience in trying to learn how to optimally treat these very challenging tumors.

Unfortunately, although a tremendous amount of work evolved evaluating these different eras of therapeutic intervention, their impact on overall outcome for patients with these tumors has been fairly modest. There is still a fair amount of interest in targeted therapies, and the whole idea of precision medicine is evolving further to try to characterize the genetic mutations associated with an individual patient's tumor and match them up with an appropriate drug to target that mutation or dysregulated cell signaling pathway.

Anti-angiogenic agents have been extensively evaluated, including in registration studies. And, although these agents have not been associated with an improvement in OS, they have had a significant impact in improving PFS, and I'd have to say on quality of life for patients with brain cancer.

The most recent era of therapeutic intervention for brain cancer in glioblastoma has focused on immunotherapies, and this is obviously an area where there is a tremendous amount of interest across a spectrum of different cancer indications. A number of immunotherapeutic drugs have now been approved for a variety of different cancer indications. Glioblastoma is not one of them—not yet—but, several ongoing studies are now evaluating a variety of different novel, innovative vaccine approaches, as well as immunomodulatory agents, such as immune checkpoint inhibitors targeting programmed death 1 (PD-1), programmed death ligand 1 (PD-L1), cytotoxic T lymphocyte antigen 4 (CTLA-4), and others. Very encouraging preclinical work has shown the efficacy of these interventions in immunocompetent syngeneic glioblastoma tumor models, and significant advanced clinical trials are now ongoing, evaluating a number of these therapeutics for patients with both newly diagnosed and recurrent disease. We are anxiously awaiting readouts from these trials, which we should be getting in the next 6 to 12 months, which we hope will put immunotherapy in the standard of care, if you will, for patients with brain cancer, as it has become for other cancer indications like melanoma, lung cancer, renal cancer, bladder cancer, and others.

Moderator: Would you discuss the challenges associated with effective drug delivery to patients with glioblastoma? What is the evidence supporting the use of FDA-approved carmustine wafer implantation? Also, what are some of the main drug delivery methods currently under investigation in glioblastoma? For example, what is the status of convection-enhanced delivery?

Dr. Reardon: Brain cancer is unique and different from other cancers in that it is not only a very challenging, aggressive,

destructive tumor, but it's unique in that we have the blood–brain barrier to overcome in order to get therapies delivered to the tumor. I'm very envious of my colleagues who focus on leukemia and melanoma and other solid tumors where the drugs can readily be administered orally or intravenously, and you can count on them being delivered effectively to the tumor.

The blood–brain barrier is a natural protective mechanism that is in place above and beyond what is present in any other organ system to protect the brain from potentially harmful or damaging agents. And that, unfortunately, frequently includes treatments for cancers. Most chemotherapies and biologically-based targeted-therapies are excluded from the central nervous system by the blood–brain barrier quite effectively.

Brain cancers, like glioblastoma, are remarkably invasive and infiltrative tumors. The reason, which nobody has ever explained, is that they do not metastasize, but they make up for that by being extremely invasive and infiltrative into the adjacent brain tissue. When I see patients in the clinic, I talk to them about their tumor and tell them that it really is composed of two different components. The first part is the main mass that we can see—the part that typically lights up with contrast. The blood–brain barrier is broken down in the enhancing part of the tumor; that is the reason that contrast persists on delayed imaging. But, in the leading edge of the tumor, where the microscopic cells are infiltrating and invading into the adjacent brain tissue, we can see swelling in some of those areas, but they typically don't demonstrate any contrast uptake. And, that's the part of the tumor—the second part of the tumor—where the blood–brain barrier is relatively intact, which is the leading edge of microscopic infiltrative disease. And, that's the part that really is most threatening to patients because it is where the tumor is growing and advancing and extending, and that's the part that is most challenging to deliver therapies to be effective against this type of cancer.

If we can only get therapies into the enhancing part of the tumor, where the blood–brain barrier is disrupted and not working properly, it is not going to help patients. The drugs, the treatments, have to effectively get into the nonenhancing, invading, infiltrating part of the tumor if we're really going to have an impact on this disease, and that has not been effectively evaluated for most therapies that are going forward for patients with brain cancer. I think that it is a deficiency that we, in the community, really need to be very proactive in addressing. We have to be more careful and deliberate about evaluating exactly how well therapies are getting into the brain, into the tumor—including, and most especially, the leading edge of nonenhancing disease—before launching into large heavily resourced trials of therapies. If therapies don't penetrate effectively, they are not going to be effective, and we really should not waste patients' time, effort, and resources in evaluating those drugs. So, I think this is a critical area where the field of neuro-oncology needs to focus and put a lot more emphasis as we develop therapies for our patients.

I think that one appealing aspect of immunotherapy is that we know that these drugs modulate immune responses against the tumor. The immune response can effectively penetrate into the brain, all areas of the brain, on an as-needed basis, and the blood–brain barrier really is not a prohibitive obstacle for that class of therapeutics.

Moderator: You and your colleagues published an article in the March 2016 issue of the *Journal of Clinical Oncology* discussing the association between the use of valproic acid or levetiracetam and survival in patients with newly diagnosed glioblastoma. Would you comment on your findings?

Dr. Reardon: There is a lot of interest on the part of patients' families, as well as treating clinicians, in trying to utilize approved drugs for repurposed treatment approaches. And, I think that there is particularly a lot of interest—fueled by the desperate need to improve outcome for patients with glioblastoma—to look at drugs that are approved for other indications to determine if they will have a therapeutic benefit by having an antitumor effect in patients with brain cancer. Historically, there has been a debate as to whether two of the more commonly utilized antiepileptic agents—valproic acid, otherwise known as Depakote, and levetiracetam, otherwise known as Keppra—have potential anticancer properties that could translate into a therapeutic benefit for patients.

There is some preclinical data to suggest valproic acid and levetiracetam, when used in the test-tube and in the Petri dish, and even in orthotopic glioblastoma animal models, could have some antitumor benefit. So, we conducted a large international meta-analysis that evaluated nearly 2000 patients who were enrolled in 4 major randomized glioblastoma trials in newly diagnosed patients and looked at outcome for all of those patients based on whether they were using any valproic acid or levetiracetam during the course of their therapy. This analysis showed that, unfortunately, the use of either of these antiepileptic drugs, although they work well to control and protect patients from seizures, was not associated with any therapeutic benefit in terms of an improved PFS or OS for these patients with newly diagnosed glioblastoma. So, I think that there may be individual subsets of patients with specific subtypes of glioblastoma for whom these agents could potentially be further evaluated, but I think that for the vast majority of patients, these data help to confirm that these are good antiepileptic agents, but unfortunately, they should not be used solely for the purpose of trying to improve outcome of the tumor, be-

cause they really do not have a therapeutic benefit.

Moderator: Numerous challenges have been identified in the design of glioblastoma clinical trials, including patient selection, monitoring immune and imaging response, and assessment of clinical outcome. Would you comment on the implications of these challenges and what progress has been made to overcome them?

Dr. Reardon: Glioblastoma is a very challenging disease that significantly impacts the neurologic function of patients, which translates into difficulties with physical function like movement, strength, dexterity, and balance. In addition, it can affect the ability to communicate with speech and reading and writing. It can affect vision. It can affect cognition—being able to think and understand—and it can affect behavior by impacting on personality. So, glioblastoma tumors, I think, are very challenging because of the breadth of impact they can have on patients, and that translates into a significant need for caregiver support and assistance for patients going forward.

These factors, I think, make it innately very challenging for patients to participate in clinical trials, and that is something we need to work harder to improve—to make clinical trials more readily available and doable for patients and families. The only way we're going to move forward and improve outcome for patients with these very challenging tumors is through well-designed clinical trials. But, patients have to be able to get to the treatment centers and be compliant with their checkups and all the tests and other things that need to be done. And, I think that it's just much more challenging for this disease, this cancer indication, than it is for most others because of the impact of the cancer on patients and the increased challenges it poses for caregivers as well.

In terms of the actual trials, going forward, we have to be very careful as we design trials to make sure that we are very articulate in the primary question we want to answer in the trial—whether it is a phase 1, a phase 2, a phase 3, or even a phase 0 trial. We also need to make sure that the appropriate patients are selected for the trial and that appropriate evaluations are conducted in terms of defining safety, as well as ultimate impact in outcome on the tumor, as the trial proceeds. Evaluating that can be very challenging. We certainly rely on the clinical status of patients, and we have recently worked very hard to develop a scale of neurologic function—called a neurologic assessment and neuro-oncology scale—that can be readily incorporated into a routine office visit. This scale was designed by a multinational group of experts to help provide a tool that could be used routinely and readily to assess the neurologic function of patients as they proceed with treatment. The scale provides a scorecard of how patients are doing neurologically with their treatment, which is critical and very important.

My patients tell me that they want to live longer, but they also prioritize wanting to live well and being able to preserve as much neurologic function as possible. So, for the first time, we have a scale that we can objectively utilize to assess how well we're doing and how well patients are doing in maintaining their neurologic function. And, then, we rely very heavily on imaging. The technology for imaging is improving and advancing, and we need to continue to make this a priority. The evaluation of brain cancers on magnetic resonance imaging (MRI) imaging can be quite challenging, particularly for therapies that can enhance an immune response or cause a fair amount of inflammation. Like immunotherapies and radiation therapy, assessment of what is happening on an MRI scan can be very muddied and difficult to assess if the tumor is actually responding or not. So, it is critical that our neuroradiology colleagues continue to work hard to advance the technology that will better allow us to accurately assess response for our patients going forward with treatment.

References

1. Ansstas G, Tran DD. Treatment with tumor-treating fields therapy and pulse dose bevacizumab in patients with bevacizumab-refractory recurrent glioblastoma: a case series. *Case Rep Neurol.* 2016;8(1):1-9. doi: 10.1159/000442196.

2. Arvold ND, Reardon DA. Treatment options and outcomes for glioblastoma in the elderly patient. *Clin Interventions Aging.* 2014;9:357-367. doi: 10.2147/CIA.S44259.

3. Cabrera AR, Kirkpatrick JP, Fiveash JB, et al. Radiation therapy for glioblastoma: an ASTRO evidence-based clinical practice guideline. *Practical Radiat Oncol.* 20166(4):217-25. doi: 10.1016/j.prro.2016.03.007.

4. Kamran N, Calinescu A, Candolfi M, et al. Recent advances and future of immunotherapy for glioblastoma. *Expert Opin Biol Ther.* 2016;16(10):1245-1264. doi:10.1080/14712598.2016.1212012.

5. McNamara MG, Sahebjam S, Mason WP. Emerging biomarkers in glioblastoma. *Cancers (Basel).* 2013;5(3):1103-1119. doi: 10.3390/cancers5031103.

6. Mrugala MM, Engelhard HH, Dinh Tran D, et al. Clinical practice experience with NovoTTF-100A™ system for glioblastoma: The Patient Registry Dataset (PRiDe). *Semin Oncol.* 2014;41(suppl 6):S4-S13. doi: 10.1053/j.seminoncol.2014.09.010.

7. Namba H, Kawaji H, Yamasaki T. Use of genetically engineered stem cells for glioma therapy. *Oncol Lett.* 2016;11(1):9-15.

8. Zhao H, Wang S, Song C, Zha Y, Li L. The prognostic value of MGMT promoter status by pyrosequencing assay for glioblastoma patients' survival: a meta-analysis. *World J Surg Oncol.* 2016;14(1):261.

9. Neagu MR, Reardon DA. An update on the role of immunotherapy and vaccine strategies for primary brain tumors. *Curr Treat Options Oncol.* 2015;16(11):54. doi: 10.1007/s11864-015-0371-3.
10. Zhou Q, Wang Y, Ma W. The progress of immunotherapy for glioblastoma. *Hum Vaccine Immunother.* 2015;11(11):2654-2658. doi: 10.1080/21645515.2015.1081727.
11. Barnholtz-Sloan JS, Maldonado JL, William VL, et al. Racial/ethnic differences in survival among elderly patients with a primary glioblastoma. *J Neurooncol.* 2007;85(2):171-180.
12. Iwamoto FM, Reiner AS, Panageas KS, Elkin BB, Abrey LE. Patterns of care in elderly glioblastoma patients. *Ann Neurol.* 2008;64(6):628-634. doi: 10.1002/ana.21521.
13. National Comprehensive Cancer Network. NCCN Clinical Practice Guidelines in Oncology. Central nervous system cancers. NCCN website. https://www.nccn.org/professionals/physician_gls/pdf/cns.pdf. Accessed October 25, 2016.
14. van Tellingen O, Yetkin-Arik B, de Gooijer MC, Wesseling P, Wurdinger T, de Vries HE. Overcoming the blood-brain tumor barrier for effective glioblastoma treatment. *Drug Resist Updat.* 2015;19:1-12. doi: 10.1016/j.drup.2015.02.002.
15. Frosina G. Advances in drug delivery to high grade gliomas. *Brain Pathol.* 2016;26(6):689-700. doi: 10.1111/bpa.12423.
16. Bienkowski M, Berghoff AS, Marosi C, et al. Clinical neuropathology practice guide 5-20-15: MGMT methylation pyrosequencing in glioblastoma: unresolved issues and open questions. *Clin Neuropathol.* 2015;34(5):250-257.
17. Stupp R, Mason WP, van den Bent MJ, et al; European Organisation for Research and Treatment of Cancer Brain Tumor and Radiotherapy Groups; National Cancer Institute of Canada Clinical Trials Group. Radiotherapy plus concomitant and adjuvant temozolomide for glioblastoma. *N Engl J Med.* 2005;352(10):987-996.
18. Roa W, Kepka L, Kumar N, et al. International Atomic Energy Agency randomized phase III study of radiation therapy in elderly and/or frail patients with newly diagnosed glioblastoma multiforme. *J Clin Oncol.* 2015;33(35):4145-4150. doi: 10.1200/JCO.2015.62.6606.
19. Zarnett OJ, Sahgal A, Gosio J, et al. Treatment of elderly patients with glioblastoma: a systematic evidence-based analysis. *JAMA Neurol.* 2015;72(5):589-596. doi: 10.1001/jamaneurol.2014.3739.
20. Cabrera AR, Kirkpatrick JP, Fiveash JB, et al. Radiation therapy for glioblastoma: executive summary of an American Society for Radiation Oncology evidence-based clinical practice guideline. *Pract Radiat Oncol.* 2016:6(4):217-225. doi: 10.1016/j.prro.2016.03.007.
21. Xia D, Reardon DA, Bruce JL, Lindeman NI. The clinical implications of inconsistently methylated results from glioblastoma MIGMT testing by replicate methylation-specific PCR. *J Mol Diagn.* 2016;18(6):864-871. doi: 10.1016/j.jmoldx.2016.06.009.
22. American Brain Tumor Association. Glioblastoma and malignant astrocytoma. ABTA website. http://www.abta.org/secure/glioblastoma-brochure.pdf. Accessed October 31, 2016.
23. Hegi ME. Diserens AC, Godard S, et al. Clinical trial substantiates the predictive value of O-6-methylguanine-DNA methyltransferase promoter methylation in glioblastoma patients treated with temozolomide. *Clin Cancer Res.* 2004;10(6):1871-1874.
24. Hegi ME, Diserens AC, Gorlia T, et al. MGMT gene silencing and benefit from temozolomide in glioblastoma. *N Eng J Med.* 2005;352(10):997-1003.
25. Iaccarino C, Orlandi E, Ruggeri F, et al. Prognostic value of MGMT promoter status in non-resectable glioblastoma after adjuvant therapy. *Clin Neurol Neurosurg.* 2015;132:1-8. doi: 10.1016/j.clineuro.2015.01.029.
26. Berghoff AS, Preusser M. Clinical neuropathology practice guide 06-2012: MGMT testing in elderly glioblastoma patients – yes, but how? *Clin Neuropathol.* 2012;31(6):405-408.
27. Wick W, Platten M, Meisner C, et al; NOA-08 Study Group of Neuro-oncology Working Group (NOA) of German Cancer Society. Temozolomide chemotherapy alone versus radiotherapy alone for malignant astrocytoma in the elderly: the NOA-08 randomised, phase 3 trial. *Lancet Oncol.* 2012;13(7):707-715. doi: 10.1016/S1470-2045(12)70164-X.
28. Malmstrom A, Gronberg BH, Marosi C, et al; Nordic Clinical Brain Tumour Study Group (NCBTSG). Temozolomide versus standard 6-week radiotherapy versus hypofractionated radiotherapy in patients older than 60 years with glioblastoma: the Nordic randomized, phase 3 trial. *Lancet Oncol.* 2012;13(9):916-926.
29. Xie H, Tubbs R, Yang B. Detection of MGMT promoter methylation in glioblastoma using pyrosequencing. *Int J Clin Exp Pathol.* 2015;8(1):636-642.
30. Friedman HS, Prados MD, Wen PY, et al. Bevacizumab alone and in combination with irinotecan in recurrent glioblastoma. *J Clin Oncol.* 2009;27(28):4733-4740. doi: 10.1200/JCO.2008.19.8721.
31. Kreisl TN, Kim L, Moore K, et al. Phase II trial of single-agent bevacizumab followed by bevacizumab plus irinotecan at tumor progression in recurrent glioblastoma. *J Clin Oncol.* 2009;27(5):740-745. doi: 10.1200/JCO.2008.16.3055.
32. Zuniga RM, Torcuator R, Jain R, et al. Rebound tumour progression after the cessation of bevacizumab therapy in patients with recurrent high-grade glioma. *J Neurooncol.* 2010;99(2):237-242. doi: 10.1007/s11060-010-0121-0.
33. Kanner AA, Wong ET, Villano JL, Ram Z, on behalf of the EF-11 Investigators. Post hoc analyses of intention-to-treat

population in phase III comparison of NovoTTF-100A System versus best physician's choice chemotherapy. *Semin Oncol.* 2014;41(suppl 6):S25-S34. doi: 10.1053/j.seminoncol.2014.09.008.
34. Carmustine implant [package insert]. Eisai, Inc: Woodcliff Lake, NJ; August 2013.
35. Brem H, Piantadosi S, Burger PC, et al. Placebo-controlled trial of safety and efficacy of intraoperative controlled delivery by biodegradable polymers of chemotherapy for recurrent gliomas. The Polymer-brain Tumor Treatment Group. *Lancet.* 1995;345(8956):1008-1012.
36. Chowdhary SA, Ryken T, Newton HB. Survival outcomes and safety of carmustine wafers in the treatment of high-grade gliomas: a meta-analysis. *J Neurooncol.* 2015;122(2):367-382. doi: 10.1007/s11060-015-1724-2.
37. Lok E, Swanson KD, Wong ET. Tumor treating fields therapy device for glioblastoma: physics and clinical practice considerations. *Expert Rev Med Devices.* 2015;12(6):717-726. doi: 10.1586/17434440.2015.1086641.
38. U.S. Food and Drug Administration. FDA approves expanded indication for medical device to treat a form of brain cancer. October 2015. FDA website. http://www.fda.gov/NewsEvents/Newsroom/PressAnnouncements/ucm465744.htm. Accessed November 6, 2016.
39. Optune [instructions for use]. Novocure. Document number:QSD-QR-703. Revision 01. Issue date: July 2016.
40. Stupp R, Wong ET, Kanner AA, et al. NovoTTF-100A versus physician's choice chemotherapy in recurrent glioblastoma: a randomized phase III trial of a novel treatment modality. *Eur J Cancer.* 2012;48(14):2192-2202. doi: 10.1016/j ejca.2012.04.011.
41. Happold C, Gorlia T, Chinot O, et al. Does valproic acid or levetiracetam improve survival in glioblastoma? A pooled analysis of prospective clinical trials in newly diagnosed glioblastoma. *J Clin Oncol.* 2016;34(7):731-739. doi: 10.1200/JCO.2015.63.6563.
42. National Cancer Institute. Genomic understanding of glioblastoma expanded. October 2013. National Cancer Institute website. https://cancergenome.nih.gov/newsevents/newsannouncements/GBM_Expanded_news_release_2013. Accessed November 8, 2016.
43. National Cancer Institute. Glioblastoma multiforme. January 2014. National Cancer Institute website. http://cancergenome.nih.gov/cancersselected/glioblastomamultiforme. Accessed October 27, 2016.
44. The Cancer Genome Atlas Research Network. Comprehensive genomic characterization defines human glioblastoma genes and core pathways. *Nature.* 2008;455(7216):1061-1069. doi: 10.1038/nature07385.
45. Brennan CW, Verhaak RG, McKenna A, et al; TCGA Research Network. The somatic genomic landscape of glioblastoma. *Cell.* 2013;155(2):462-477. doi: 10.1016/j.cell.2013.09.034.
46. Preusser M, Lim M, Hafler DA, Reardon DA, Sampson JH. Prospects of immune checkpoint modulators in the treatment of glioblastoma. *Nat Rev Neurol.* 2015;11(9):504-514. doi: 10.1038/nrneurol.2015.139.
47. Desai R, Suryadevara CM, Batich KA, Farber SH, Sanchez-Perez L, Sampson JH. Emerging immunotherapies for glioblastoma. *Expert Opin Emerg Drugs.* 2016;21(2):133-145. doi: 10.1080/14728214.2016.1186643.
48. Swartz AM, Li QJ, Sampson JH. Rindopepimut®: a promising immunotherapeutic for the treatment of glioblastoma multiforme. *Immunotherapy.* 2014;6(6):679-690. doi: 10.2217/imt.14.21.